REMARKS

Amendments

Applicant thanks Examiner Epps for the telephone interview granted to Applicant's attorneys on May 16, 2003 regarding certain potential patentability issues (not of record) of the pending claims over U.S. Patent Nos. 5,514,788 (hereafter "Bennett, et al."), 5,733,572 (hereafter "Unger, et al.") and 6,207,646 (hereafter "Krieg, et al."), which the Examiner had requested Applicant's attorneys to consider during the intereview.

Claim 260 is amended by adding the phrase "of about 0.5 μm to 500 μm in size". Support for this amendment is found, for example, in original Claims 181 and 182 as filed.

Claim 260 is amended by replacing "up to about 15%" with "10% or less". Support for this amendment is found, for example, in page 40, lines 25-26.

Claim 261 is cancelled.

Claims 262 and 263 are amended by deleting "up to about" before the percent figure and adding "or less" after it. This amendment is to clarify the language so the claims are more definite within the meaning of 35 U.S.C. § 112, second paragraph.

Claim 276 is amended to make Claim 276 an independent claim.

Claims 260 and 262-276 are pending. Applicant respectfully contends that the amendments will place the application in condition for allowance. No new matter is added in any of the above amendments and the Examiner is respectfully requested to enter the amendments and reconsider the application.

Response

The pending claims are novel and non-obvious over Bennett, et al., Unger, et al., and Krieg, et al.

Applicant respectfully submits that Claims 260 and 262-276 are novel and non-obvious over Bennett, et al., Unger, et al., and Krieg, et al.

Bennett, et al. disclose therapeutical treatments involving the use of antisense oligonucleotides that specifically hybridize with nucleic acids encoding ICAM-1, VCAM-1 and ELAM-1, proteins involved with intercellular adhesion. Bennett, et al. disclose examples using such oligonucleotides in cell cultures (for example, col. 19, Example 19) and also by

intravenous infusion of such oligonucleotides into mice to reduce inflammatory bowel disease in a murine model system (col. 26, Example 20), to increase survival in murine heterotopic heart transplant model (col. 26, Example 21), and to decrease leukocyte migration caused by exposure to carrageenan (col. 26-28, Example 22). Bennett, et al. state in the "Background of the Invention": "It is has been **hoped** that inhibitors of ICAM-1, VCAM-1 and ELAM-1 expression would provide a novel therapeutic class of anti-inflammatory agents with activity towards a variety of inflammatory diseases or diseases with an inflammatory component such as asthma . . ." (col. 3, lines 13-17; emphasis added). It is clear from the language that Bennett, et al. are merely opining about the desirability of having "inhibitors of ICAM-1, VCAM-1 and ELAM-1 expression" capable of treating asthma. However, Bennett, et al. do not provide sufficient teaching to enable any antisense oligonucleotides for treating diseases such as asthma.

Unger, et al. disclose using microspheres, with biocompatible lipids or polymers skins encapsulating a gas or gaseous precursor, for topical and subcutaneous administration of drugs or cosmetics (col. 5, lines 43-46; col. 6, lines 48-54). Unger, et al. disclose that, of the microspheres produced using the method of Example 1 (col. 50-51), it "should be determined that the largest size of the microsphere ranges from about 50 to about 60 μm" while "the smallest size detected should be about 8 μm" (col. 50, lines 49-52).

Krieg, et al. disclose using immunostimulatory oligonucleotides containing CpG unmethylated dinucleotides to redirect a Th2 response to a Th1 response. Krieg, et al. disclose examples using such oligonucleotides in cell cultures (for example, col. 39-41, Example 10) and also by **injection** of such oligonucleotides into mice to prevent development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma (col. 42, Example 12). Krieg, et al. do not disclose the use of any antisense oligonucleotide.

Bennett, et al., Unger, et al., and Krieg, et al. do not render obvious a method of delivering to the airways of a subject an oligonucleotide that is of respirable or inhalable particle size, wherein the oligonucleotide has a relatively low level of adenosine.

MPEP 2144.08 states: "[T]he claimed invention may not be dissected into discrete elements to be analyzed in isolation, but must be considered as a whole. See, e.g., W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983); Jones v. Hardy, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1983) ("treating the advantage as

the invention disregards the statutory requirement that the invention be viewed `as a whole'")."

The court in *Deuel* (51 F.3d at 1557, 34 USPQ2d at 1214) stated that: "[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original). The court in *In re Lalu* (747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984)) stated that: "The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."

MPEP 2144.8 (II) (A) (4) (a) states that: "Some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g., Deuel, 51 F.3d at 1558-59, 34 USPQ2d at 1215 ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); Baird, 16 F.3d at 382-83, 29 USPQ2d at 1552; Bell, 991 F.2d at 784, 26 USPQ2d at 1531 ("Absent anything in the cited prior art suggesting which of the 1036 possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.")."

Bennett, et al., Unger, et al. and Krieg, et al., either alone or combined, do not teach or suggest administering to the airways of a subject a pharmaceutical composition of a respirable or inhalable particle size, especially a particle size of about 0.5 μm to 500 μm in size comprising an oligonucleotide to alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy, and especially where the oligonucleotide has 10% or less adenosine. In particular, Applicant particularly points out that none of these disclosures teach the advantage of using an oligonucleotide of 10% or less adenosine in order to alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy. There is no motivation or suggestion provided in these references to select the oligonucleotides having low levels of adenosine. None of these disclosures teach or suggest using these oligonucleotides with low levels of adenosine are suitable for preventing the "untoward side effects of adenosine-mediated hyperresponsiveness in certain individuals, which are generally seen in diseases affecting respiratory activity" (page 7, lines 22-24). One of the discoveries of the inventor is using a low (or reduced) adenosine content oligonucleotide (page 38, lines 11-14) to alleviate hyper-

responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy. That Bennett, et al. and Krieg, et al. disclose a few examples (out of over 80 in Bennett, et al. and over 50 in Krieg, et al.) of oligonuclotides that happen to have 15% or less of adenosine does not suggest or motivate one to arrive at the presently claimed invention. There is no teaching or motivation for one skilled in the art to use an oligonucleotide of 10% or less adenosine. Such molecules enable one to alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy. The priori art contains no such teaching or motivation.

Further, Bennett, et al. disclose antisense oligonucleotides, but there is no direct teaching of using such molecules in the manner instantly claimed or the small particle size claimed; much less a reasonable expectation that administering the antisense oligonucleotides of Bennett, et al. would be effective in treating diseases such as asthma. Krieg, et al do not even disclose any antisense oligonucleotide. The immunostimulatory oligonucleotide (containing CpG unmethylated dinucleotides) of Krieg, et al. do not anticipate the claimed method. Since the oligonucleotides of Bennett, et al. and Krieg, et al. are so different (the former's functions using an antisense mechanism, while the latter acts as an immunostimulant), there is no suggestion or motivation to combine the disclosure of these two patents. Unger, et al. does not cure the deficiency of Bennett, et al. and Krieg, et al. One skilled in the art would have to rely on improper hindsight reasoning in order to arrive at the subject matter of Claims 260 and 262-276.

For the foregoing reasons, Claims 260 and 262-276 are novel and non-obvious over Bennett, et al., Unger, et al. and Krieg, et al.

CONCLUSION

In view of the foregoing amendment and remarks, the Applicant believes that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 463-8109.

Respectfully submitted,

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